SUMMARY OF INTERVIEW

Date of Interview

June 29, 2006

Exhibits and/or Demonstrations

None

Identification of Claims Discussed

Claims relating to 35 U.S.C. § 112 rejections were discussed. Independent Claims 1 and 12 were discussed in reference to 35 U.S.C. § 103 rejections.

Identification of Prior Art Discussed

U.S. Patent No. 6,207,193, issued March 7, 2001, to Frank C. Pellegrini (hereinafter "the '193 patent").

Proposed Amendments

Applicants' representative proposed amending the claims to address section 112 issues.

Principal Arguments and Other Matters

Applicants' representative asserted that the claims distinguish the claimed invention over the '193 patent. Applicants' representative and Examiner Ghali discussed the differences between the '193 patent and the present claims, and in particular the encapsulation of the active agent and the polymerization inhibitor taught in the '193 patent. Applicants' representative and Examiner Ghali also discussed disclosure in the specification and proposed revisions to the claims to address section 112 rejections. At the conclusion of the interview, Applicants' representatives agreed to submit an amendment that incorporates revisions regarding at least some of the section 112 rejections, and that includes arguments distinguishing the '193 patent as agreed to in the interview.

Results of Interview

Applicants' representatives agreed to amend the claims and present arguments in accordance with the points raised during the discussion with Examiner Ghali.

REMARKS

Claim 1-6, 8, 10-12, 14-18, 20, 22-24, 26-29, 31-34 are pending in this application. Claims 1 and 12 have been amended. Support for the amendments is found in the specification and claims as filed and is discussed below. Applicants thank Examiner Isis Ghali for the courteous and helpful interview conducted with Applicants' representative Gregory A. Hermanson on June 29, 2006. In response to the Office Action, and in accordance with the interview conducted on June 29, 2006, Applicants submit the foregoing amendments and provides remarks addressing the claim rejections indicated in the Office Action.

Claim Rejection 35 U.S.C. § 112, First Paragraph

The Office Action indicated claims 1-6, 8, 10-12, 14-18, 20, 22-24, 26-29, and 31-34 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Office Action also indicates the claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Office Action also states "the amendments made to claims 1 and 12 have introduced new matter and applicants failed to point out support for the amendment.
Each § 112 rejection is addressed below:

"liquid adhesive"

Paragraph No. 4 of the Office Action states, in part,

> [t]he specification has failed to describe anywhere "liquid adhesive." Applicants have disclosed adhesive not in the liquid state. On page 20, lines 1-7 of the originally filed specification, applicants disclose that 2-cyanoacrylic ester monomers are liquids, while cyanoacrylates used for medical use are of longer alkyl chain, i.e., butyl and octyl; and this disclosure does not support that the presently claimed butyl and octyl cyanoacrylate that have long alkyl chain are liquid. Additionally, even if the cyanoacrylate is liquid, this does not support that the adhesive composition comprising cyanoacrylate and other ingredients are also liquid specifically the claimed composition comprises polyethylene glycol that is known as a thickening agent and may change the viscosity of the adhesive composition as a whole.

Applicants traverse this rejection.

As discussed in the interview, Applicants respectfully assert that there is sufficient description in the specification that the adhesive is a "liquid" and that the adhesive in a pre-polymerized state is disclosed to be in a "liquid state." For example, in describing a preparation of use, the specification discloses the cyanoacrylate and microcapsule mixture as having "fluidity" for a period of time, which is consistent with the disclosure of the cyanoacrylate adhesive as a liquid that can have different viscosities. (Specification page 20, lines 1-11). Specifically, the specification states the

> [c]yanoacrylate is drawn into the syringe, which is shaken to thoroughly mix the adhesive and microcapsules. The mixture thus obtained may be extruded through a needle of suitable size. If the seal cap is put back onto the syringe, the *mixture is able to maintain its fluidity* for a period of time, typically 4 hours or more. (Specification page 36, lines 18-21).

Accordingly, Applicants respectfully assert that the specification sufficiently discloses that before polymerization the cyanoacrylate adhesive (mixture) is a liquid, and Applicants respectfully request this section 112 rejection be withdrawn.

"protective shell"

The Office Action states the "expression 'protective shell' is not supported by the disclosure, applicants disclosed on page 11, line 18 'shell', not 'protective shell'." Applicants traverse this rejection, and respectfully assert that "protective shell" is disclosed in the specification on page 11 line 25-27, which states "Microencapsulation techniques involve the coating of small particles, liquid droplets, or gas bubbles with a thin film of a material, the material providing a protective shell for the contents of the microcapsule." Accordingly, Applicants respectfully request this section 112 rejection be withdrawn.

"chemical reaction"

> Paragraph No. 4 of the Office Action states, in part,
>
> [t]he expression "chemical reaction" is not supported by the disclosure, applicants disclosed on page 11, lines 20-21 that "shells block undesired reactions," not "chemical reactions." Applicants only disclosed on page 11, lines 11-13 that "other substances may be sensitive to the components of cyanoacrylate adhesive

and as a result may undergo adverse reaction," and this disclosure does not support "the shell is configured to block chemical reaction."

Applicants traverse this rejection and respectfully assert that there is sufficient disclosure to support the use of the phrase "chemical reaction." For example, the specification discloses that "[m]icroencapsulation is an effective technique to avoid undesired chemical interaction between medicaments and cyanoacrylates" (specification page 11, lines 15-16). However, to facilitate timely prosecution of this application, the foregoing amendments to claims 1 and 12 include that the microcapsule shell blocks "undesired reactions" as disclosed in the specification (page 11, line 20). Accordingly, Applicants respectfully request this section 112 rejection be withdrawn.

"substantial premature curing of the adhesive is prevented"

Paragraph No. 4 of the Office Action states, in part, "[a]pplicants did not disclose that 'substantial premature curing of the adhesive is prevented', what applicants disclosed on page 11, lines 9-11 is 'cyanoacrylate adhesive may contain reactive groups that activate the polymerization of cyanoacrylic esters, resulting in premature curing of the adhesive.'"

Applicants traverse this rejection and respectfully assert that there is sufficient disclosure that substantial premature curing of the adhesive is prevented by using a microcapsule shell "that blocks undesired reactions by substantially preventing direct contact of the antibiotic and the cyanoacrylate." (Claim 1 and 12). In the section captioned "Microencapsulated Medicaments," the specification particularly identifies undesired chemical reactions of "premature curing of the adhesive" (page 11, line 11) and "failure of adhesives by solidification during storage" (page 11, lines 13-14) as problems. The disclosure specifically states reactive groups (in medicaments, pharmaceutical compositions, and therapeutic agents) can "activate the polymerization of cyanoacrylic esters, resulting in premature curing of the adhesive." (Page 11, lines 8-11). In the same section, the specification discloses a solution to avoid undesired chemical interaction (e.g., premature curing) by preventing contact between the medicaments and the cyanoacrylate using microencapsulation (page 11, 15-16), "[m]icroencapsulation is an effective technique to avoid undesired chemical interaction between medicaments and cyanoacrylates" (page 11, lines 15-16) and that the "microcapsules' shells block undesired reactions by substantially preventing direct

contact of the antibiotics and cyanoacrylates" (page 11, lines 19-21). For clarity and to address the section 112 rejections, Applicants' foregoing amendments to claims 1 and 12 include language to more closely conform to the wording used in the specification. Such amendments are supported at least by the disclosure on page 11, lines 8-24. Accordingly, Applicants respectfully request this rejection be withdrawn.

"the microcapsules are configured to provide controlled release"

Paragraph No. 4 of the Office Action states, in part, the "Applicants did not disclose that 'the microcapsules are configured to provide controlled release', Applicants disclosed on page 11, lines 23-24 that '[t]he microencapsulated antibiotics provide long-term controlled release". The foregoing amendments amend claims 1 and 12 to include "long-term controlled release." Accordingly, Applicants respectfully request this section 112 rejection be withdrawn.

"antibiotics are entrapped into hydrophilic gelatin microcapsules"

Paragraph No. 4 of the Office Action states, in part, that "applicants disclosed on page 11, lines 17-18 that 'antibiotics are entrapped into hydrophilic gelatin microcapsules', while claims 1 and 12 do not recite gelatin, and nowhere Applicants disclosed antibiotics encapsulated in other types of microcapsules." Applicants traverse this rejection. Applicants disclose microcapsules comprising gelatin (as stated above) as well as many other materials, for example, "water soluble alcohols and polyethylene oxides (specification page 11, line 19) and "gum arabic, gelatin, ethycellulose, polyurea, polyamide, aminoplasts, maltodextrins, and hydrogenated vegetable oil" (specification page 12, lines 18-20). Accordingly, Applicants respectfully request this section 112 rejection be withdrawn.

Rejection of Claims 1-5, 8, 12, 14-17, 20, 27-29, and 32-34 Under 35 U.S.C. § 103(a)

Claims 1-5, 8, 12, 14-17, 20, 27-29, and 32-34 have been rejected under 35 U.S.C. § 103(a) as unpatentable over WO 96/10,374 (hereinafter "WO '374") in view of U.S. Patent number 6,207,193 ('939). Applicants traverse this rejection. To articulate a *prima facie* case of obviousness under 35 U.S.C. § 103(a), the PTO must, *inter alia*, cite prior art that teaches or

suggests all the claimed limitations. *In re Royka*, 490 F.3d 982 (C.C.P.A. 1974); MPEP §2143.03.

As discussed in the interview on June 29, 2006 and as summarized in the remarks below, the cited references do not, either singly or in combination, teach or disclose all the elements of amended claims 1 and 12, shown below:

> A stable liquid adhesive for sealing a wound, the adhesive comprising:
> a cyanoacrylate; a therapeutic agent comprising an antibiotic;
> a defect forming agent capable of being removed from a cured cyanoacrylate matrix by solvation in an aqueous solution whereby a plurality of defects in the matrix are formed permitting release of the therapeutic agent from the matrix at a controlled rate; and
> a microcapsule encapsulating said antibiotic, the microcapsule comprising a protective shell that blocks undesired reactions by substantially preventing direct contact of the antibiotic and the cyanoacrylate to avoid premature curing of the adhesive, and wherein the microcapsule provides long-term controlled release of the antibiotic from the cured cyanoacrylate matrix. (Claim 1).
>
> A method of sealing a wound, the method comprising the steps of:
> approximating the wound;
> applying a liquid adhesive comprising a mixture of a cyanoacrylate, a therapeutic agent comprising an antibiotic encapsulated in a microcapsule, and a water soluble defect forming agent to a tissue surface surrounding the wound, the microcapsule comprising a protective shell that blocks undesired reactions by substantially preventing direct contact of the antibiotic and the cyanoacrylate;
> curing the adhesive, whereby the wound is sealed;
> removing the defect forming agent from the cured adhesive by solvating the defect forming agent in a body fluid, whereby a plurality of defects in the cured adhesive are formed; and
> delivering the antibiotic to the wound through the defects in the cured adhesive at a controlled rate, wherein the microcapsule provides long-term controlled release of the antibiotic from the cured adhesive. (Claim 12).

WO '374 teaches an adhesive composition comprising cyanoacrylate, PEG (a pore forming agent), and an active substance (e.g., an antibiotic). The '193 patent teaches a transdermal drug delivery system that includes "a drug or therapeutic agent encapsulated in a carbohydrate...being suspended in a cyanoacrylate ester" ('193 Col. 2, 54-58). However, neither the WO '374 or the '193 reference discloses or teaches a "microcapsule comprising a protective shell that blocks

undesired reactions by substantially preventing direct contact of the antibiotic and the cyanoacrylate" (Claims 1 and 12) which avoids problems of premature curing (polymerization and solidification) of the cyanoacrylate (as disclosed in the specification, page 11, lines 8-21).

As noted in the Office Action, the reference (WO '374) "does not teach encapsulating the active substance." Although the '193 patent discloses a drug encapsulation technique, encapsulation in the '193 patent does not "*substantially prevent direct contact* of the antibiotic and the cyanoacrylate" as claimed in claims 1 and 12. In the '193 patent, the drug is dissolved or suspended in a molten carbohydrate matrix which is then cooled to form a glass-like matrix. The glass-like matrix is pulverized into micro-fine sized particles which are then suspended in a cyanoacrylate ester ('193 Col. 3, 51-58). Because the drug is dissolved or suspended throughout the matrix, when the matrix is pulverized into micro-fine particles, portions of the drug are not encapsulated, instead residing on the surface or only partially encapsulated in the micro-fine particle. There is no teaching in the '193 patent of using encapsulation to avoid the problem of premature curing, and specifically no teaching to "substantially prevent *direct contact* of the drug and the cyanoacrylate" to avoid premature curing. The '193 patent only teaches that the "drug delivery system results in a time release of the drug or therapeutic agent into the body system." (The '193 patent, col. 4, 23-34). In fact, the cyanoacrylate mixture taught in the '193 patent identifies the problem of premature curing, and recognizes that its disclosed encapsulation technique does not prevent premature polymerization because the '193 patent teaches the mixture also includes "polymerization inhibitors to increase the stability of the cyanoacrylate ester and prolong shelf life...a suitable polymerization inhibitor that can be used is sulfur dioxide" ('193 Col. 3, 37-44). The encapsulation technique and the resulting microcapsule formed in the '193 is completely different than claimed in the present application, where, for example, "a coating is sprayed or otherwise deposited in the filler material particles so as to form a shell" (specification page 13, lines 3-4) where the "microcapsules' shells block undesired reactions by *substantially preventing direct contact* of the antibiotics and the cyanoacrylates" (specification page 11, lines 19-21).

Applicants discovered that cyanoacrylate adhesive mixtures having a microcapsule that substantially prevents direct contact of the antibiotic and the cyanoacrylate blocks undesired

chemical interactions and avoids premature curing (polymerization and solidification) of the cyanoacrylate. Encapsulation also facilitates controlled release of the antibiotic from the cured cyanoacrylate adhesive through defects in the cured adhesive provided by solvation of the defect forming agent. The cited references, alone or in combination, do not teach or suggest such features of the cyanoacrylate adhesives as claimed.

Accordingly, Applicants respectfully request that this claim rejection be withdrawn for claims 1 and 12 and assert claims 1 and 12 are in condition for allowance. Because claims 2-5, 8, 14-17, 20, 27-29, and 32-34 depend from claims 1 and 12 either directly or indirectly, Applicants also respectfully request that this claim rejection be withdrawn for claims 2-5, 8, 14-17, 20, 27-29, and 32-34, and assert that these claims are also in condition for allowance.

Rejection of Claims 10, 11, 23, and 24 under 35 U.S.C. § 103(a)

Claims 10, 11, 23, and 24 have been rejected under 35 U.S.C. § 103(a) as unpatentable over WO '374 in view of the '193 patent and further in view of WO 96/00760 (WO '760). Applicants traverse these rejections for at least the reason that claims 10 and 11 depend from claim 1 and claims 23 and 24 depend from claim 12, which are asserted to be in condition for allowance as discussed above. After a careful review of the art, Applicants respectfully assert that the addition of WO '760 includes no additional disclosure overcoming the deficiencies of the WO '374 reference and the '193 patent in disclosing or teaching all the limitations of claims 1 and 12, nor does the Office Action state that it does. Instead, WO '760 merely discloses biomedical adhesives comprising a biocompatible pH modifier (*e.g.*, a microencapsulated pH modifier). Accordingly, Applicants request that this rejection be withdrawn and respectfully assert claims 10, 11, 22, and 23 are in condition for allowance.

Rejection of Claims 6 and 8 under 35 U.S.C. § 103(a)

Claims 6 and 8 have been rejected under 35 U.S.C. § 103(a) as unpatentable over WO '374 in view of the '193 patent and further in view of WO 99/20685 (WO '685). Applicants traverse these rejections for at least the reason that claims 6 and 8 depend from claim 1, which are asserted to be in condition for allowance as discussed above. After a careful review of the

art, Applicants respectfully assert that the addition of WO '685 includes no additional disclosure overcoming the deficiencies of the WO '374 reference and the '193 patent in disclosing or teaching all the limitations of claims 1 and 12, nor does the Office Action state that it does. Instead, WO '685 merely discloses coating formulations for sustained-release drug implants that include pore forming agents. Accordingly, Applicants request that this rejection be withdrawn and respectfully assert claims 6 and 8 are also in condition for allowance.

Rejection of Claims 26 and 31 under 35 U.S.C. § 103(a)

Claims 26 and 31 have been rejected under 35 U.S.C. § 103(a) as unpatentable over WO '374 in view of the '193 patent and further in view of 5,695,779 ('779). Applicants traverse these rejections for at least the reason that claims 6 and 8 depend from claims 1 and 12, respectively, which are asserted to be in condition for allowance, as discussed above. After a careful review of the art, Applicants respectfully assert that the addition of '779 includes no additional disclosure overcoming the deficiencies of the WO '374 reference and the '193 patent in disclosing or teaching all the limitations of claims 1 and 12, nor does the Office Action state that it does. Accordingly, Applicants request that this rejection be withdrawn and respectfully assert claims 26 and 31 are also in condition for allowance.

Conclusion

Applicant has endeavored to address all of the Examiner's concerns as expressed in the outstanding Office Action. In view of the foregoing amendments and remarks, reconsideration and withdrawal of the outstanding rejections is respectfully requested, and it is respectfully asserted that the present application is in condition for allowance.

Any claim amendments which are not specifically discussed in the above remarks are not made for patentability purposes, and it is believed that the claims would satisfy the statutory requirements for patentability without the entry of such amendments. Rather, these amendments have only been made to increase claim readability, to improve grammar, and to reduce the time and effort required of those in the art to clearly understand the scope of the claim language. They

are simply additional specific statements of inventive concepts described in the application as originally filed.

Should the Examiner have any remaining concerns that might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number below, or contact Greg Hermanson at (619) 687-8610.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 7/27/06

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